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HIV-infection modeling

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Abstract: In the paper a problem of stabilizing a HIV infection dynamics mathematical model is considered. The model is described by a system of functional differential equations. A stabilizing control is constructed basing on the method of explicit solutions of Generalized Riccati Equations of the theory of analytical constructing regulator for systems with delays. For construct a feedback control we use the first variant of explicit solutions of the generalized Riccati equations (the study of control stabilizing properties based on other variants discussed in other authors articles). Stabilizing control for the system of differential equations with delay supports HIV-infection model spread at a certain sufficiently small non-zero level. Results of the research can be applied to analysis of some aspects of HIV dynamics.

Keywords: modelling; HIV; differential equations with delay; generalized Riccati equations.

1. INTRODUCTION

It has been over 30 years since the discovery of human immunodeficiency virus (HIV) as the causative agent of AIDS. Today, the HIV pandemic has affected about 35 million people worldwide. Even if successful viral suppression with highly active antiretroviral therapy (Arts, 2012), the infection can not be completely cured. Moreover, so far not developed an effective vaccine (Kwong, 2011; Jang, 2011). The reasons for this are directly related to two important features of HIV. Firstly, the HIV provirus can be hidden in the target cell (T-cells) and therefore remain undetected by the immune system and drug used. Secondly, the variability of HIV may lead to the emergence of drug resistance in immune recognition and reduced (Arts, 2012). The advent of modern methods of investigation led to an understanding of the importance of specific factors of the human body to support or limit HIV replication. In particular, the current research is aimed at the source of the depletion of latent HIV (Cohen, 2011).

Beginning with the work of G.I. Marchuk and R.V. Khokhlova, mathematical modeling is an important part of a serious immunological research. Broad classes of mathematical models that adequately describe the dynamics of HIV allow mathematical tools to analyze the immune processes and develop appropriate methods.

One of the most interesting and important problems in mathematical immunology is to develop methods of control immune models, as progress in this direction, given the current level of experimental and clinical studies can, with sufficient funding and proper management, to translate research into practical management of HIV dynamics.

In this paper we consider the problem of constructing the feedback control, stabilizing the HIV model, the mathematical model described by a system of linear functional differential equations that allows you to apply for the construction of control theory analytical construction of regulators for systems with (Kwon, 2010; Krasovskiy, 1962; Kim, 1998). In Kwon (2010) and Kim (1998) based on the explicit solution of the generalized Riccati equation obtained several options for feedback control for linear systems with delays. This approach is used to study the problem of stabilization of the considered model of HIV. In the first part of the paper examines stabilizability HIV infection model, built on the basis of a first embodiment of explicit solutions GRE. In the second part of the research applied management, built on the basis of a third embodiment of explicit solutions GRE. Computer simulations showed that both control stabilize consider HIV model.

1.1 HIV-infection mathematical model

Classical mathematical model HIV-infection spread in the human body is a system of differential equations with delay (Bocharov, 2012; Ciupe, 2006):

$$\begin{cases} \dot{T}(t) = s - dT - kVT, \\ \dot{T}^*(t) = kVT - \delta T^* - d_x ET^*, \\ \dot{V}(t) = N\delta T^* - cV, \\ \dot{E}(t) = pT^*(t-\tau) - d_E E, \end{cases},$$

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$$\begin{cases} \dot{T}(t) = s - dt - kVT \\ \dot{T}^*(t) = kVT - \delta T^* - d_X E T^* \\ \dot{V}(t) = N\delta T^* - cV \\ \dot{E}(t) = pT^*(t-\tau) - d_E U \end{cases} \quad (1)$$

where $T(t)$ - number of uninfected T-cells,

$T^*(t)$ - number of infected T-cells,

$V(t)$ - number of free viral cells,

$E(t)$ - immune response, the number of effector cells generating by human body after drug stimulation,

s - source of healthy cells,

d - healthy cells mortality,

p - effector cells activation rate,

k - the rate of infection,

b - infected cells mortality,

d_x - immune response effectiveness,

N - number of virus particles obtained from one infected cell,

c - viral cells clearance,

d_E - effector cell mortality,

τ - (delay) - time required effector cell for infection recognition,

U - drug immune response stimulation that help human body generate effector cells and kill free viral cells in human blood.

The process regulation can be carried out at the expense of drug enhancing the immune response: in this case U is a control parameter of $u(t)$.

The parameters of the system (1) are presented in (Ciupe, 2006)

$$\mathrm{T}(0) = \mathrm{T}_0, \mathrm{T}^*(\varphi) = 0, \mathrm{V}(0) = \mathrm{V}_0, \mathrm{E}(0) = 0,\ \varphi \in [-\tau, 0],$$
$$T_0 = 10,\ T^*_0 = 0,\ V_0 = 10^{-9},\ E_0 = 0.1,$$
$$s = 0.103,\ d = 0.01025,\ p = 1.473,\ c = 0.557,$$
$$k = 0.0000065,\ b = 0.514,\ d_x = 0.812,\ N = 2500,$$
$$d_E = 1.618,\ \tau = 16.05,$$
$$\overline{V} = -729.2579,\ \overline{T}^* = -0.3161,\ \overline{E} = -0.2878,\ \overline{T} = 18.6939$$

System (1) can be conveniently represented in matrix form as (Ciupe, 2006)

$$\dot{x}(t) = Ax(t) + A_\tau x(t-\tau) + Bu(t), \quad (2)$$

$$A = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -3 & 0 & 3 \\ 0 & 1285 & -6 & 0 \\ 0 & 0 & 0 & -16 \end{bmatrix},$$

$$A_\tau = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 1.473 & 0 & 0 \end{bmatrix},$$

$$B = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}.$$

The system (2) has a root with a positive real part (Ciupe, 2006) and is unstable (El'sgol'ts, 1971). The considered task is to construct a feedback control

$$u[t, x(t), x(t+s)] = Cx(t) + \int_{-\tau}^{0} \mathrm{E}(s)x(t+s)ds, \quad (3)$$

stabilizing system (3). As mentioned above is not always HIV-infected cells may be derived from the human body, however, in contrast to the technical concept of the stabilization, when the solution tends to zero, we understand the following stabilization.

Control (3) β-stabilizes ($\beta \in R^n$) system (2), if system (2) is β-asymptotically stable, i.e. every decision of this closed system tends to β.

1.2 The purpose and methodology of research

The purpose of this paper is to simulate the process of HIV replication in the human body and research the properties of stabilizing feedback control, that was built on the basis of a first variant of explicit solutions GRE.

In Krasovskiy (1962), Kim (1996, 1998, 2004, 2011) and Kwon (2010) discuss how stabilizing control on the basis of generalized Riccati equation explicit solutions.

A first variant of explicit solutions GRE (Kwon, 2010) corresponds to the feedback control

$$u^*(x, y(\cdot)) = -N^{-1}B'\left[Px + \int_{-\tau}^{0} e^{-[PK - A']'(s+\tau)} PA_\tau y(s)ds \right], \quad (4)$$

and closed system

$$\dot{x}(t) = Ax(t) + A_\tau x(t-1) - K * \left[Px + \int_{-\tau}^{0} e^{-[PK - A']'(s+\tau)} PA_\tau y(s)ds \right], \quad (5)$$

This control is obtained by substituting (4) into the original system (2). There is

$$K = BN^{-1}B'.$$

In control (4), the 4×4 matrix P is a solution of the matrix equation (Kim, 2004)

$$PA + A'P + M = PKP, \quad (6)$$

where M - the identity matrix.

To verify that the control (4) β-stabilizes system (2) is sufficient to show β-asymptotically stability of the closed system

$$\dot{x}(t) = (A - BN^{-1}B'P)x(t) + A_\tau x(t-\tau) + \\ + \int_{-\tau}^{0} (G(s) - BN^{-1}B'e^{-[PK-A']'(s+\tau)}PA_\tau)x(t+s)ds. \quad (7)$$

2. COMPUTER SIMULATION RESULTS

2.1 Solution of the matrix equation

Solution of equation (6) can be found analytically and equal

$$P_1 = \begin{bmatrix} 0 & 41 & 0 & 1 \\ 41 & 11767 & 41 & 315 \\ 0 & 41 & 0 & 1 \\ 1 & 315 & 1 & 11 \end{bmatrix}. \quad (8)$$

2.2 System trajectory construction

The trajectory of the system (4) (see Figure 1) converges to β, and hence control (4) is β-stabilizes.

When $\tau = 16.05$ the system (5) tends to

$$\beta = \begin{bmatrix} 2.5930 \\ -0.001 \\ -2.3601 \\ 0.0479 \end{bmatrix}.$$

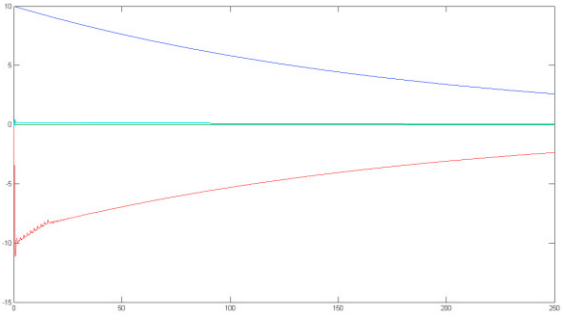

Fig. 1. The trajectory of the system (5).

In the case of using the control (4) for stabilizing the system (5) can be observed a significant (to a negative value) reduction count of free viral cells in the human body ($V(t)$ parameter in the (1) system of functional differential equations).

The number of infected T-cell ($T^*(t)$ parameter in the (1) system of functional differential equations) is stabilized at a low level negative value.

Control leads system (5) to a steady state with low viral load and a small amount of infected T-cells and can to stabilize system (5) in state with negative values of these parameters. These factors can be attributed to the positive results of application control, built on the first variant explicit solutions of generalized Riccati equation.

The negative consequences using control (4) for stabilizing the system (5) is reducing the number of effectors and uninfected T-cells ($E(t)$ and $T(t)$ parameters in the system of functional differential equations).

This inevitably occurs reduction in the immune functions of the human organism as a whole. With long-term using of stabilization may occur development immunopathological processes that ultimately can lead to autoimmune diseases and hypersensitivity to various infections.

In order to reduce the negative impacts of the considered control is proposed to apply it is not continuous, but discrete. Period of application of immune drugs offered alternate with recover periods.

This approach will significantly increase the amount of time needed to lead the system to a steady state, but will reduce the negative effects of therapy.

3. CONCLUSION

Thus, the feedback control is constructed on the basis of a first variant of generalized Riccati equation explicit solutions is β-stabilizes the spread of HIV-infection in humans.

At the same control characteristics tend to some non-zero value. That is, the control maintained replication of HIV-infection in the human body in a certain steady state.

This steady state is characterized by low level of infected T-cells and viral loads, but also human body immune function is in depressed state.

To reduce the negative impact of therapy on the human body are encouraged to apply discrete control, although this approach will increase the total time to lead the system in a steady state.

Comparing our results with the results of other authors Ciupe (2006), Jang (2011), Kwong (2011), Arts (2012), it should be noted that the considered control, built on the basis of a first variant of generalized Riccati equations explicit solutions not only leads the (1) system of functional differential equations describing the HIV-infection model dynamics in the human body, in a steady state with low viral load and allows to achieve remission of the disease at a level not dangerous to human life, but also can contribute to the complete disappearance of free viral cells and infected T-cells.

Remains an open the question about stabilizing properties of controls, built on the basis of the second and third variant of explicit solutions of generalized Riccati equations.

Subsequent articles will be considered building a stabilizing control on the basis of the remaining variants of explicit solutions GRE and discuss the results of their using for stabilizing the HIV-infection dynamics model that was built in the current article.

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